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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/623,970	Applicant(s) KARUBE ET AL.	
	Examiner Lisa Gansheroff	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) 7-20 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Pending claims: 1-20.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-6 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that, according to Applicants: all groups are closely related and would require common areas of search and consideration and no benefit is derived from maintaining the restriction requirement. This is not found persuasive because the different groups require searches that are not coextensive, and the evaluation of the search results would differ for the different groups, as would other aspects of examination. Thus, it would be a severe burden on the Examiner to have to examine the multiple distinct inventions in one application, and thus there is benefit in maintaining this proper restriction requirement.

The requirement is still deemed proper and is therefore made FINAL.

Claims 7-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

International Search Report

The Examiner has considered the references cited in the International Search Report.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of denaturing or perforating a specific site of a membrane using a photosensitizing compound and light stimulation, or other methods known in the art (see below), does not reasonably provide enablement for the full scope of combinations of compounds and specific stimulations to denature/perforate a membrane. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in determining that the specification does not enable the skilled artisan to practice the invention commensurate in scope with the claims.

The nature of the invention. The invention is complex because in order to denature or perforate a specific site of a membrane, the method requires a combination of a reagent containing a compound that induces a membrane-denaturing reaction by a specific stimulation and also said stimulation.

The state of the prior art and the predictability or unpredictability of the art. The prior art teaches combinations of photosensitizing compounds and light stimulation; see rejections under 35 USC 102 below. The prior art also teaches combinations of a reagent containing a compound such as polyethylene glycol and a stimulation of a bacterial protoplast (see rejection under 35 USC 102 below; it is noted that in the instant specification on page 9 that the stimulation used can include cells and viruses, and thus it is considered that a protoplast of a bacteria is encompassed by the instant claims). However, the prior art also teaches many ways

of perforating/denaturing a specific site on a membrane that requires only a stimulation or a compound, but not both; for example, Sambrook et al. (pages 16.30-16.31) teach methods of introduction of vectors (DNA) into cells, which requires perforating the membrane so as to get the DNA into the cell, by means of electroporation, which uses electricity, and by microinjection, as well as other methods. However, while electricity and physical contact (microinjection) are listed as "stimulations" on page 9 of the instant specification, it seems that no accompanying "specific compounds" are required in combination in the art; that is, electricity in the context of electroporation will perforate a membrane without the need for a compound that "induces a membrane-denaturing reaction", and likewise, microinjection apparently also does not require such a compound. Thus, it is unpredictable, in the art, what sort of "specific compound" could be used in combination with the various disclosed stimulations of the instant application, when these stimulations alone are sufficient. Further, it is unpredictable what compounds exist that, in combination with other stimulations, would achieve the method of the instant claims.

The amount of direction or guidance presented in the specification and the presence or absence of working examples. The specification contemplates many different "stimulations", including radiation, heat, cooling, electricity, magnetism, ultrasonic waves, viruses, and so forth (page 9), and many different "compounds", including explosive compounds such as nitroglycerin, antibody molecules, glycoproteins, lipids, magnetic particulates, metal particles, and so forth (page 9). The specification also states that " as to the combination of the compound and stimulation used for denaturing or perforating the membrane, any combination may be used" (page 9). However, the specification only lists different compounds and different stimulations without stating which combinations will work (page 9). With the exception of the

combination of photosensitizing compounds and light, there is no guidance in the specification or working examples as to other combinations of compounds and stimulations. The specification, then, invites the person of skill in the art to experiment to invent new combinations of compounds and stimuli that are not contemplated in the instant specification.

The breadth of the claims. The claims are extremely broad. The claims encompass an apparently infinite number of possible "specific compounds", which can be anything from "glycoproteins" (although it is not stated, for example, which "specific" glycoproteins would be useful, if any) to "explosive compounds" and so forth, and a huge number of possible "stimulations", which can be anything from viruses to ultrasonic waves, to cooling, and so forth. The claims also encompass an extremely broad number of different types of "membranes"; see pages 9-10, in which "membrane" can encompass cell membranes, metal membranes, electric conductive high molecular (polyacetylene) membranes, etc.

The quantity of experimentation. Based on the complex nature of the invention, the state of the prior art, the unpredictability of the art, the lack of sufficient guidance or working examples in the specification, and the breadth of the claims, an undue amount of experimentation is required for one of skill in the art to practice the claimed invention commensurate with its full scope. Not only would the skilled artisan have to perform undue experimentation to invent different combinations of a specific compound plus a specific stimulation, but also the artisan would have to perform undue experimentation to determine which such combinations would work for different types of "membranes" that could be anything from a biological cell membrane to metal.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1-5 are drawn to a genus of methods using combinations of a specific compound plus a specific stimulation which result in denaturing or perforating a specific site of a membrane. The disclosure only teaches one such combination, that of photosensitizing compounds plus light stimulation. The disclosure also lists various other compounds, such as antibodies, glycoproteins, nitroglycerin, and so forth, and provides a list of various stimulations, including cooling, ultrasonic waves, chemical substances, and so forth, without contemplating, for example, which specific glycoprotein or antibody in combination with which specific stimulation would work. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the combination of a photosensitizing compound plus light stimulation alone is insufficient to describe the genus, especially considering that the genus also encompasses a huge variety of membranes from biological membranes to "metal membranes" and electric conductive high molecular membranes (see pages 9-10). One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a "specific" site of a membrane, a "specific" compound, and a "specific" stimulation. The term "specific" renders the claims indefinite because it indicates that a "specific" site, compound, and stimulation are intended, but there is no recitation in the claim of what the actual site, compound, and stimulation are. While claim 6 recites light and a photosensitizing compound as specific stimulation and compound, it does not identify what the "specific site" is to be.

Claims 3 and 4 recite the limitation "the region" (twice in each claim). There is insufficient antecedent basis for this limitation in the claims.

Claim 6 recites that "the reagent is contacted using a support". This phrase is indefinite, because it is not clear what the support is for; that is, it is not clear in the claim language whether it is to be a support for the reagent or a support for the membrane, and how it is used. Also, since claim 1 recites contacting the membrane with the reagent, it would be more clear to recite consistent phraseology in dependent claim 6 and state that the membrane is contacted with the reagent, rather than that the "reagent is contacted".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the

basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Thorpe et al. (1995. Biophysical Journal 68:2198-2206, on Applicant's IDS). The claims are drawn to a method of denaturing or perforating a specific site of a membrane comprising contacting the whole or part of the membrane with a specific compound and giving a specific stimulation; the compound and stimulation can be a photosensitizing compound and light.

Thorpe et al. teach denaturing or perforating a specific site of a membrane comprising contacting the membrane with a reagent containing a photosensitizing compound (tin chlorin e6) and giving light stimulation. Thorpe et al. teach that the cell membrane ruptured (denatured or perforated) at a single point (page 2202, right column, and page 2205, last paragraph), and thus the method denatured/perforated a specific site on the membrane. Thorpe et al. also teach using a support for contacting the reagent containing the specific compound: the photosensitizing compound was linked to a monoclonal antibody for use in antibody target photolysis; the monoclonal antibody is used as a carrier for the photosensitizer, and thus is a support for it (see page 2198, first column of Introduction, and page 2199, Chemicals and biochemicals section). Since the membrane was ruptured, inherent in the method is that the region stimulated is included in the region contacted with the reagent, and vice versa.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Valenzo (1987.

Photochemistry and Photobiology 46:147-160, on Applicant's IDS).

Valenzo teaches a method for perforating a specific site of a membrane comprising contacting the membrane with a reagent containing a photosensitizing compound and giving light stimulation (see pages 147-149). Valenzo teaches a method comprising denaturing or perforating a specific site of an *E. coli* membrane comprising contacting the membrane with a reagent (medium) containing the photosensitizing compound "rose bengal" using a support which is polystyrene beads, and then photoinactivation occurred, indicating light stimulation was given. The contacting comprised putting the *E. coli* into the same medium as the rose bengal bound to the polystyrene beads. Valenzo teaches that a singlet oxygen can diffuse a finite distance in solution to photomodify (denature or perforate) the membrane (page 149). The specific site of the membrane that is perforated or denatured would be the specific site attacked by a diffusing singlet oxygen or, possibly, a specific site that contacted the rose bengal on the polystyrene beads directly. Valenzo also teaches association (contacting) of photosensitizer compounds with membranes, including cell membranes, artificial membranes (liposomes), and so forth, and giving light stimulation (see for example pages 150-151). Since in the teachings of Valenzo the membranes were denatured or perforated, the region contacted with the reagent inherently included the region stimulated, and vice versa. Thus, Valenzo anticipates the instant claims.

Claims 1-4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Morgan (GB 2 209 468 A, on International Search Report).

Morgan teaches perforating or denaturing a specific site on a membrane (liposome) by

contacting the membrane with a photosensitising agent and then giving light stimulation. The method results in destabilization of the lipid bilayer and fusion between liposomes and/or exchange of membrane bound constituents between liposomes and/or cells or fusion of liposomes with cells. Since the liposomes can fuse, they are not completely destroyed, and thus inherent in the method of Morgan is that a specific site of the membrane is perforated or denatured (rather than the entire liposome). The region contacted with the reagent included the region stimulated, and vice versa. See Abstract and pages 5 and 6.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Sambrook et al. (Molecular cloning, a laboratory manual, Cold Spring Harbor: Cold Spring Harbor Laboratory Press, 1989, pages 16.30-16.31 and 16.48-16.53).

Sambrook et al. teach a method of denaturing or perforating a specific site of a cell membrane comprising contacting the membrane with the compound polyethylene glycol and giving the specific stimulation of a bacterial cell protoplast. See pages 16.30-16.31 and 16.48-16.53. The result of the method is that DNA is transferred from the bacterial protoplast into a mammalian cell, with the protoplast fused to the mammalian cell; thus, the cell membrane is denatured/perforated at the specific site of protoplast fusion. It is noted that on page 9 of the instant specification, a cell is contemplated as a specific stimulation; thus it is construed that a protoplast of a bacterial cell is encompassed by the claims as a stimulation; page 13 of the specification also teaches that the invention may be applied for cell fusion, using substances such as polyethylene glycol. Since there was fusion, the region contacted with the reagent included the region stimulated, and vice versa.

Claims 1-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Saito (1998, Photochemistry and Photobiology 68(5):745-748).

Saito et al. teach a method of denaturing/perforating a specific site of a membrane comprising contacting the membrane with a reagent containing a photosensitising compound (BAT) and giving light stimulation. Since membrane damage was achieved, the region contacted with the reagent included the region stimulated, and vice versa.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa J. Gansheroff whose telephone number is (703) 605-1203. The examiner can normally be reached 9 AM - 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242 for regular communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Dianiece Jacobs whose telephone number is (703) 305-3388 or to the receptionist whose telephone number is (703) 308-0196.

LG
July 8, 2001

JAMES KETTER
PRIMARY EXAMINER